1083-8791/07/1302-0001$32.00/0
doi:10.1016/j.bbmt.2006.09.012

ASBMT
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Systematic Review of Controlled Clinical Trials on the Use of Ursodeoxycholic Acid for the Prevention of Hepatic Veno-occlusive Disease in Hematopoietic Stem Cell Transplantation

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Received July 6, 2006; accepted September 27, 2006

ABSTRACT

Hepatic veno-occlusive disease (HVOD) is a serious life-threatening complication of hematopoietic stem cell transplantation (HSCT). Currently, there is no optimal therapeutic strategy and preventive measures are ill-defined. Ursodeoxycholic acid (UA) is well-tolerated oral medication that has been associated with possible benefit as a prophylactic agent. We sought to summarize and quantify the clinical effects of prophylactic UA in the context of HSCT. We undertook a systematic review of studies addressing the use of UA as monotherapy or in combination with other agents in patients undergoing HSCT. The Search Strategy included MEDLINE (1966 to fourth week of March 2006), EMBASE (1980 to fourth week of March 2006), all EBM Reviews (fourth quarter of 2005), Ovid Healthstar (1966 to fourth week of March 2006), and Google Scholar on March 20, 2006. Six studies, 4 randomized clinical trials and 2 historically controlled studies, representing 824 patients were included in the review. Three randomized clinical trials comparing prophylactic UA with no treatment demonstrated reduced proportion of HVOD (relative risk [RR], 0.34; 95% confidence interval [CI], 0.17-0.66). When the analysis was limited to higher-quality studies, the beneficial effect of UA remained significant (RR, 0.36; 95% CI, 0.15-0.90). Transplant-related mortality was also reduced with the prophylactic use of UA (RR, 0.58; 95% CI, 0.35-0.95). UA did not significantly attenuate the outcomes of acute graft-versus-host disease (RR, 0.76; 95% CI, 0.53-1.09), relapse (RR, 0.77; 95% CI, 0.46-1.31), or overall survival (RR, 1.22; 95 % CI, 0.96-1.54). UA appears effective for HVOD prophylaxis in patients undergoing HSCT and should be considered as a prevention strategy by HSCT centers to reduce HVOD.

KEY WORDS

Hepatic sinusoidal obstruction syndrome • Veno-occlusive disease • Prophylaxis • Hematopoietic transplantation • Ursodeoxycholic acid

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a common therapy in the management of hematologic malignancies [1]. Preparative regimens often involve the use of myeloablative chemotherapy with or without total body irradiation, which can contribute to profound endothelial injury and the development of hepatic veno-occlusive disease (HVOD), also known as hepatic sinusoidal obstruction syndrome. HVOD remains a major contributor to transplant-related toxicity and mortality, with incidence rates reported as high as 50% in some series and mortality rates that can approach 50% [2,3].

HVOD is characterized by tender hepatomegaly, jaundice, and ascites [4]. If left untreated, HVOD can lead to cardiopulmonary compromise, liver failure, and death. HVOD is thought to occur as a result of hepatic venous endothelial injury, leading to occlusion

of terminal venous venules and sinusoids. Further, the use of hepatotoxic drugs in the setting of HSCT can augment the severity of liver dysfunction in HVOD. Several risk factors for HVOD have been identified and include a history of liver disease, increased aspartate aminotransferase levels before transplantation, decreased pseudocholinesterase levels, use of HLA-mismatched donors, and previous abdominal irradiation [5,6].

The diagnosis of HVOD is most often made clinically because histologic examination is infrequently sought due to concerns related to hemostatic control in these patients. The Seattle [7] or Baltimore [8] criteria are clinical criteria used to aid in the diagnosis of HVOD. Using a histologic diagnosis as "gold standard," Carrreras et al [9] showed that, although the specificity of the Seattle criteria may be as high as 92%, its sensitivity may be as low as 56% even if all 3 criteria are satisfied. The more stringent Baltimore criteria performs as well as the Seattle criteria but selects a group of patients with more severe HVOD and a poorer prognosis [10]. To complicate matters, the diagnosis of HVOD may not be obvious and may be confounded by multiple competing diagnoses such as hepatic graft-versus-host disease (GVHD) [11,12].

The successful management of HVOD involves preventive measures and/or treatment of the disease. When feasible, hepatotoxic medications should be avoided or minimized and prior liver disease optimized before transplantation. However, no therapy has been shown to be satisfactory in the treatment of established HVOD. Prevention strategies and pharmacologic prophylaxis are critical to reduce morbidity and mortality from HVOD. Several candidate pharmacologic agents have been reported to be useful, including ursodeoxycholic acid (UA), heparin molecules [13], prostaglandins [14], glutamine [15], and defibrotide [16]. The relative benefits and safety of these agents remain unclear, leading to various center-dependent management strategies.

UA occurs naturally in bile and has an important role in controlling the concentration of cholesterol in the blood. It constitutes <5% of naturally occurring bile acids and can be increased to 50% with oral administration [17]. UA is a hydrophilic bile acid and is used for the dissolution of gallstones [18] and in the management of primary biliary cirrhosis [19-21]. It is believed that the retention of endogenous hydrophobic bile acids contributes to hepatocellular injury in patients with cholestatic liver disease. UA appears to alter the milieu of bile acids by making them less hydrophobic, resulting in decreased hepatotoxicity [22]. Moreover, additional evidence has suggested that UA may attenuate the pro-inflammatory cytokine environment through decreased expression of tumor necrosis factor α, interleukins 1 and 2, and interferon γ [23], thereby minimizing endothelial injury occurring in HSCT associated with the "cytokine storm."

In the context of HSCT, UA has been used as prophylaxis and treatment for HVOD and GVHD. In the earliest studies describing its use in transplantation, UA was used in the management of chronic GVHD, with evidence that it can normalize liver function tests [24-26]. Likewise, early studies in the treatment of HVOD showed promise and resulted in several larger studies exploring its role in HSCT [27-30]. Notably, the Nordic Bone Marrow Transplantation group in a randomized study of >200 patients demonstrated beneficial effects of prophylactic UA in reducing the proportion of patients with transaminitis, hyperbilirubinemia and a trend toward a reduction in acute GVHD [31]. However, they were not able to demonstrate decreases in clinical outcomes such as HVOD. Subsequent studies have focused on the use of UA in the prevention of HVOD and several randomized studies have been performed. No clear consensus exists on the role of UA in preventing HVOD despite these studies and no common approach has been universally adopted by HSCT centers.

Given the potential benefits of UA that are particular to HSCT and the current lack of consensus regarding pharmacologic prophylaxis of HVOD, we conducted a systematic review of the published literature to summarize and quantify the clinical effects of the prophylactic use of UA in patients undergoing HSCT.

METHODS

A systematic literature search strategy was used to identify potential trials on MEDLINE (1966 to fourth week of March 2006), EMBASE [16] (1980 to fourth week of March 2006), all EBM Reviews (fourth quarter of 2005), and Ovid Healthstar (1966 to fourth week of March 2006). A search of "gray literature" was also performed using Google Scholar. The systematic search strategy is documented in Table 1. Studies relevant to animals but not to humans were excluded. Published studies in any language were included. Axcan Pharma (Canadian manufacturer of UA) was contacted to identify any additional relevant articles/trials that were not cited in the previous search. Similarly, local bone marrow transplantation physicians were approached to identify any other relevant trials/articles. References of selected articles were examined by 2 reviewers (JT and DA) to identify relevant citations.

Using a structured question format (PICOS) to aid our literature search strategy [32], we identified trials that satisfied the following inclusion criteria: controlled clinical trials, patients undergoing HSCT, patients receiving UA prophylaxis, use of a comparator arm, studies reporting clinical outcomes (HVOD

Table 1. *Medline Search Strategy*

1. ursodeoxycholic acid.mp. [mp=ti, ot, ab, nm, hw]
2. ursodiol.mp. [mp=ti, ot, ab, nm, hw]
3. ursofalk.mp. [mp=ti, ot, ab, nm, hw]
4. actigall.mp.
5. UDCA.mp.
6. URSO.mp.
7. URSO 250.mp.
8. deoxycholic acid.mp.
9. destolit.mp.
10. urdox.mp.
11. ursogal.mp.
12. hematopoietic stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
13. hematopoietic peripheral blood stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
14. haematopoietic stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
15. haematopoietic peripheral blood stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
16. peripheral blood cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
17. peripheral blood stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
18. stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
19. bone marrow transplant$.mp. [mp=ti, ot, ab, nm, hw]
20. marrow transplant$.mp. [mp=ti, ot, ab, nm, hw]
21. peripheral stem cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
22. blood transplant$.mp. [mp=ti, ot, ab, nm, hw]
23. peripheral blood progenitor cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
24. progenitor cell transplant$.mp. [mp=ti, ot, ab, nm, hw]
25. HSCT.mp. [mp=ti, ot, ab, nm, hw]
26. SCT.mp. [mp=ti, ot, ab, nm, hw]
27. PBPCT.mp. [mp=ti, ot, ab, nm, hw]
28. BMT.mp. [mp=ti, ot, ab, nm, hw]
29. veno occlusive disease.mp. [mp=ti, ot, ab, nm, hw]
30. VOD.mp. [mp=ti, ot, ab, nm, hw]
31. Sinusoidal Obstruction.mp. [mp=ti, ot, ab, nm, hw]
32. SOS.mp [mp=ti, ot, ab, nm, hw]
33. Sinusoidal Obstruction Syndrome [mp=ti, ot, ab, nm, hw]
34. Rokitansky's Disease.mp. [mp=ti, ot, ab, nm, hw]
35. Budd's Syndrome.mp. [mp=ti, ot, ab, nm, hw]
36. Chiari's Disease.mp. [mp=ti, ot, ab, nm, hw]
37. Budd Chiari Syndrome.mp. [mp=ti, ot, ab, nm, hw]
38. Chiari Budd Syndrome.mp. [mp=ti, ot, ab, nm, hw]
39. Graft versus host disease.mp. [mp=ti, ot, ab, nm, hw]
40. graft vs host disease.mp. [mp=ti, ot, ab, nm, hw]
41. GVH$.mp. [mp=ti, ot, ab, nm, hw]
42. Runt Disease.mp. [mp=ti, ot, ab, nm, hw]
43. Homologous Wasting Disease.mp. [mp=ti, ot, ab, nm, hw]
44. runting disease.mp. [mp=ti, ot, ab, nm, hw]
45. or/1-11
46. or/12-28
47. or/29-38
48. or/39-44
49. or/46-48
50. 45 and 49

or VOD), overall survival (OS), transplant-related mortality (TRM), GVHD. Publications in any language, conference proceedings, abstracts, or journals were included in our review. Clinically important outcomes defined for this review are HVOD, GVHD, and mortality. Studies that only reported results of biochemical tests were excluded from our review.

The definition of HVOD was defined as weight gain or fluid accumulation, elevated bilirubin, and abdominal pain. TRM was defined as death within 100 days of HSCT and OS as survival >100 days.

Two reviewers independently applied the inclusion criteria to the identified articles from the initial search strategy. Articles for potential full review were discussed between the 2 reviewers. Any discrepancies were noted and the decision to include/exclude the article(s) was adjudicated by a third party (DF).

Two reviewers (JT and DA) assessed trial quality and extracted the data using a standardized data abstraction form. Any discrepancies were documented, discussed, and adjudicated by a third party (DF). The methodologic quality of randomized studies was evaluated by 2 reviewers (JT and DA) using a validated 5-point system as proposed by Jadad et al [33]. This validated scale demonstrates good inter-rater reliability and its components consist of description of study being randomized, study described as double blind, description of dropouts and withdrawals, and a thorough description of randomization and blinding. A quality score ≥ 3 was considered high quality. Trial quality was further assessed with the use of standardized questions related to trial methodology such as allocation concealment [34].

Relative risk (RR) was used as the primary summary measurement with 95% confidence intervals (CIs). Pooled measurements were calculated for randomized clinical trials using a random effects model. Individual trial estimates and pooled estimates were performed with Review Manager software (Cochrane Collaboration's Information Management System). The Cochrane Q/chi-square test and I^2 statistic were also calculated to evaluate consistency.

RESULTS

In total, 161 articles were identified by the systematic search of the literature and 13 articles were deemed potentially eligible. Seven of these studies were excluded from the review. Four studies were abstracts of articles included in the review [29,30,35,36]. One study did not use a comparator group [37]. One study investigated the treatment of HVOD [28] and 1 study looked at biochemical surrogate outcome only [26].

Subsequently, 6 articles met our inclusion criteria (Figure 1). There were no discrepancies between the 2 reviewers with regard to studies for inclusion. Of the 6 clinical trials included in this review [22,27,31,38-40], 1 clinical trial specifically evaluated a pediatric population [40], and the other 5 were conducted in adults [22,27,31,38,39]. Two studies in-

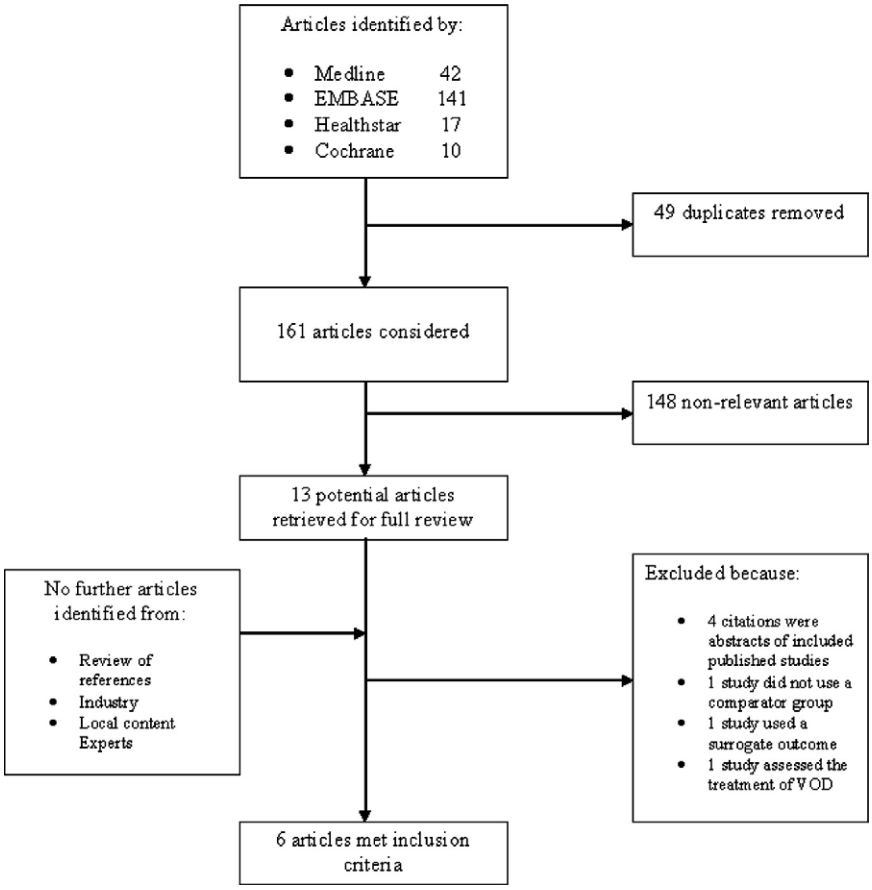

Figure 1. Flow diagram summarizing the identification process of relevant clinical trials. VOD indicates veno-occlusive disease.

cluded patients undergoing allogeneic or autologous transplantation [38,39]. The remaining 4 studies focused on patients undergoing allogeneic transplantation only [22,27,31,40]. Four of the 6 clinical trials were randomized [22,31,38,39], with the remaining 2 using historical controls [27,40]. No randomized study received a score >3 on the Jadad scale. Only 1 of the 4 randomized studies reported on allocation concealment [22] and only 1 study was double blinded [22]. (Table 2).

There were 824 patients from all studies included for analysis, with a median sample of 149 patients (range, 59-242 patients). Four studies compared UA with no treatment [22,27,31,38], 1 study compared combination therapy (including UA) with no treatment [40], and 1 study compared combination therapy using heparin and UA with heparin alone [39]. The baseline characteristics were similar apart from age addressed in the pediatric trial. Important baseline characteristics and risk factors for HVOD are presented in Tables 3 and 4. The definitions of HVOD used in the 6 trials were relatively similar when using the Seattle criteria, Baltimore criteria, or a variant of the 2 criteria (Table 5).

All 6 trials reported on the primary outcome of interest: proportion of patients with HVOD. Four studies reported TRM [22,27,31,39], 3 studies reported OS [31,38,40], and 4 studies reported rates of acute GVHD [22,27,31,40]. Relapse was reported by 3 studies [22,31,38], but only 2 provided numerical details [22,31] (Table 5). Although sensitivity and subgroup analyses were planned, the small number of studies limited the number of analyses.

Primary Outcome: VOD

The results of using UA alone as prophylaxis in HSCT compared with no treatment were pooled from 3 randomized studies and demonstrated a RR of 0.34 (95% CI, 0.17-0.66; Figure 2). The single study by Park et al [39] that compared combination of UA and heparin with heparin alone did not demonstrate a benefit (RR, 0.82; 95% CI, 0.42-1.60). Similarly, a study by Thornley et al [40] comparing the combination of multivitamins with UA showed no statistically significant benefit (RR, 0.19; 95% CI, 0.03-1.35). A randomized study by Essell et al [22] comparing UA with no treatment with a Jadad score ≥3 was significant (RR, 0.36; 95% CI, 0.15-0.90). No differences were found between studies which reported exclusively on recipients of allogeneic HSCT versus studies of patients undergoint allogeneic and autologous HSCT (data not shown).

Table 2. *Study Quality Assessment Tool*

Quality Assessment of Individual Trials	Essell et al [27]	Essell et al [22]	Ohashi et al [38]	Park et al [39]	Ruutu et al [31]	Thornley et al [40]
Are the objectives of the study clearly stated?	+	+	+	+	+	+
Is the study design suitable/reasonable for the objectives?	+	+	+	+	+	+
Were the inclusion criteria clear?	+	+	−	+	+	+
Was a sample size calculation performed?	NA	+	+	−	+	−
Was the sample size justified by the authors?	NA	+	−	NA	−	NA
Were all subjects accounted for?	+	+	+	+	+	+
Were appropriate outcomes considered?	+	+	+	+	+	+
Was ethical approval obtained?	+	+	NS	+	NS	+
Was the study randomized?	−	+	+	+	+	−
Was the randomization described and appropriate?	NA	−	−	+	−	NA
Was there adequate allocation concealment?	NA	+	NS	NS	NS	NA
Was the study double blinded?	NA	+	−	−	−	NA
Was blinding described?	NA	+	NA	NA	NA	NA
Were dropouts (if any) described?	NA	NA	+	+	+	NA
Was intention-to-treat analysis used?	NA	NA	−	+	−	NA
Are the outcomes clinically relevant?	+	+	+	+	+	+
Were the outcomes clearly defined?	+	+	+	+	+	+
Are the baseline data adequately described?	+	+	+	+	+	+
Were the groups comparable at baseline?	+	+	+	+	+	+
Are the results internal consistent? Numbers add up?	+	+	+	+	+	+
Were there side effects reported?	−	−	−	+	+	+
Are the data suitable for analysis?	+	+	+	+	+	+
Are the methods appropriate to the data?	+	+	+	+	+	+
Was the statistics correctly interpreted?	+	+	+	+	+	+
Are the authors' conclusion justified?	+	+	+	+	+	+
Jadad scores for randomized trials	NA	3	2	3	2	NA

NA indicates not applicable; +, yes; −, no; NS, not stated.

Publication bias was assessed using a funnel plot that compared the RR of HVOD with the standard error for each study (Figure 3). The funnel plot showed no significant asymmetry.

Secondary Outcomes

Three of the 4 trials that reported on TRM compared UA with no treatment, 2 of which were randomized studies [22,31]. The pooled RR for the 2 randomized trials was 0.58 (95% CI, 0.35-0.95). Park et al [39] compared the combination of UA and heparin with heparin alone and reported an RR of 1.24 (95% CI, 0.54-2.03; Figure 4).

Three studies reported OS. The pooled RR of the 2 randomized controlled trials was 1.15 (95% CI, 0.94-1.41), whereas the historical controlled study demonstrated an RR of 1.44 (95% CI, 1.09-1.89; Figure 4).

Four studies reported on acute GVHD. Two randomized trials compared UA with no treatment. The historical controlled study by Thornley et al [40] evaluated combination therapy with UA versus no treatment, and study by Essell et al [27] compared UA with no treatment. The pooled RR for the 2 randomized trials was 0.76 (95% CI, 0.53-1.09; Figure 4).

Relapse was reported in 3 studies, with complete data available from only 2 (Figure 4) [22,31]. Both studies with complete data were randomized and compared UA with no treatment. The pooled summary RR was 0.77 (95% CI, 0.46-1.31; Figure 4).

DISCUSSION

Our systematic review demonstrates that prophylactic UA significantly reduces the proportion of HVOD in patients undergoing allogeneic HSCT (RR, 0.34; 95% CI, 0.17-0.66). The reduction of HVOD also resulted in lower TRM (RR, 0.36; 95% CI, 0.35-0.95), although a reduction in OS was not observed (RR, 1.15; 95% CI, 0.94-1.41). A trend toward lower rates of disease relapse (RR, 0.77; 95% CI, 0.45-1.31) and acute GVHD (RR, 0.76; 95% CI, 0.53-1.09) was observed but did not reach statistical significance. Increased number of patients may be required to achieve sufficient power to draw conclusions regarding these important clinical events. Further, despite the beneficial prophylactic effects of UA in attenuating short-term toxicity including HVOD and TRM, later outcomes such as relapse and OS are influenced by factors that extend beyond the early regimen-related toxicities [41].

Our review identified relatively few controlled studies with modest samples; however we were able to demonstrate a favorable clinical effect of UA on re-

Table 3. *Characteristics of Included Studies*

Study/ Country	Centers, n/Study Design	Patients, n		Age (y)		Gender (% Male)		Conditioning Regimen		Intervention	
		Experimental Arm	Control Arm	Experimental Arm	Control Arm	Experimental Arm	Control Arm	Experimental Arm	Control Arm	Experimental Arm	Control Arm
Essell et al [27]/USA	1/non-RCT (historical control)	28	22	Mean 33.2 (range 11-57)	Mean 39 (range 19-61)	77%	61%	Bu/Cy	Bu/Cy	600 mg (<90 kg), 900 mg (>90 kg) OD PO from day −7 to day +80	None
Essell et al [22]/USA	1/RCT	32	35	Mean 38 (range 22-56)	Mean 37 (range 21-56)	63%	63%	Bu/Cy	Bu/Cy	600 mg (<90 kg), 900 mg (>90 kg) OD PO started before HSCT to day +80	None
Ohashi et al [38]/Japan	9/RCT	67	65	Mean 34.5	Mean 35.7	60%	46%	Chemotherapy based 23 (Bu/Cy and Bu/VP16, 18); chemotherapy + TBI 34; chemotherapy + TLI 10	Chemotherapy based 18 (Bu/Cy and Bu/VP 12); chemotherapy + TBI 37; chemotherapy + TLI 10	600 mg OD PO from day −21 to day +80	None
Park et al [39]/Korea	1/RCT	82	83	Median 39	Median 38	50%	48%	Variety used: with TBI 27, with Bu/Cy 13, others 42	Variety used: with TBI 31, with Bu/Cy 16, others 36	900 mg OD PO from day −1 to day +30 and heparin 5 IU/(kg · h)	Heparin 5 IU/(kg · h)
Ruutu et al [31]/Finland	3/RCT	123	119	Median 38 (range 5-59)	Median 40 (range 1-58)	50%	43%	TBI based 112, chemotherapy only 11, Bu 6, ATG 56	TBI based 107, chemotherapy only 12, Bu 11, ATG 51	12 mg/(kg · d) PO from day −1 to day +30	None
Thornley et al [40]/USA	1/non-RCT (historical control)	37	131	Median 8 (range 0.7-19)	Median 8 (range 0.4-22)	NR	NR	TBI based 33	TBI based 113	15 mg/(kg · d) PO from day −1 to day +27, folinic acid, vitamin E, and parenteral nutrition	None

RCT indicates randomized controlled trial; Bu/Cy, busulfan/cyclophosphamide; TBI, total body irradiation; TLI, total lymphoid irradiation; HSCT, hematopoietic stem cell transplantation; OD, once daily; PO, orally; VP16, etoposide; ATG, antithymocyte globulin; NR, not reported.

Table 4. *Important Clinical Characteristics in Included Studies*

Study	Patients with Increased LFTs (≤7 d of HSCT)		Previous Chemotherapy		Previous Liver Disease		Mean Total Dose of Busulfan		Mean Total Dose of MTX	
	Experimental Arm	Control Arm	Experimental Arm	Control Arm	Experimental Arm	Control Arm	Experimental Arm	Control Arm	Experimental Arm	Control Arm
Essell et al [27]	5	0	NR	NR	5	1	1 mg/kg q6h for 4 d	1 mg/kg q6h for 4 d	27.7 mg/kg	27.5 mg/kg
Essell et al [22]	3	3	10	10	10	6	17 mg/kg (0.75-0.875 mg/kg q6h for 4 d)	17 mg/kg (0.75-0.875 mg/kg q6h for 4 d)	29 mg/kg	26 mg/kg
Ohashi et al [38]	Reported as NS	Reported as NS	2 previous HSCT	2 previous HSCT	Reported as NS	Reported as NS	NR	NR	NR	NR
Park et al [39]	Reported as NS	Reported as NS	NR	NR	Reported as NS	Reported as NS	NR	NR	NR	NR
Ruutu et al [31]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thornley et al [40]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

LFT indicates liver function test; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; NS, not significant; NR, not reported.

ducing the incidence of HVOD by pooling the results of the 3 randomized trials comparing UA with no treatment. The results of the randomized trial by Park et al [39] were not included in the overall summary measurement of results from the other randomized controlled trials concerning our primary outcome. We could not substantiate an assumption of no interaction between the combination of UA and heparin in the experimental arm of the study by Park et al, leading us to exclude these results from the pooled estimates obtained from the other studies. If one includes the results from Park et al in the pooled estimate, the reduction in HVOD remains significant (data not shown). The beneficial effects of UA on reducing HVOD appear to also contribute to improved rates of TRM.

The study populations from the studies included in our systematic review are heterogeneous in terms of the conditioning chemotherapy and the dosing of UA. In particular, the studies by Essell et al used predominantly busulfan and cyclophosphamide as conditioning agents, whereas the remainder of studies used a variety of regimens, largely excluding busulfan. Despite the differences, the test for heterogeneity is not significant ($P < .002$) and the I^2 is 0% for our primary outcome derived from the 3 randomized studies comparing UA with no treatment, suggesting that overall heterogeneity is low and exerting minimal effect on the pooled estimate of HVOD prevention using UA.

Busulfan is commonly employed as conditioning therapy in patients undergoing myeloablative allogeneic HSCT and is associated with increased risk of developing HVOD [42]. This likely contributes to the increased proportion of patients in the control arm of the studies by Essell et al [22,35] who developed HVOD as busulfan was used in all patients. In addition, it is worth noting that the definition of HVOD used by Essell et al may include patients with less severe disease, thus contributing to the larger proportion of HVOD in the control arm. The baseline incidence of HVOD in control arms of the other studies included in our analysis is appreciably lower. Patients who received busulfan as part of the conditioning regimen in the studies by Ohashi et al and Ruutu et al were 20% and <10%, respectively (Table 3). Moreover, we suggest the relative beneficial effects of UA may be similar regardless of baseline risk (Figure 5), indicating that UA may benefit a heterogeneous group of patients.

The use of pharmacologic prophylaxis to reduce HVOD and the toxicity of transplantation must be considered in concert with the changing risk factors for HVOD. With the appreciation that busulfan is a risk factor for HVOD, serum busulfan levels can be measured to guide adjustments in dosing, thereby potentially reducing toxicities associated with variable bioavailability and pharmacokinetics observed be-

Table 5. *Definitions and Reported Outcomes of Included Studies*

Study	Follow-up Duration	HVOD Definition*	Reported Outcomes					
			VOD	TRM	OS	aGVHD	cGVHD	Relapse
Essell et al [27]	NR	McDonald/Seattle criteria	+	+	−	+	−	−
Essell et al [22]	Mean 42 mo	<30 d after HSCT and 2 of 3: bilirubin >3 mg/dL, painful hepatomegaly, fluid accumulation (ascites or >5% weight gain)	+	+	−	+	−	+
Ohashi et al [38]	Median 182 d	2 of 3: bilirubin >2.0 mg/dL, painful hepatomegaly, fluid accumulation (ascites or >2% weight gain)	+	−	+	−	−	Yes, but specifics not provided
Park et al [39]	100 d	Modified Seattle criteria	+	+	−	−	−	−
Ruutu et al [31]	≥1 y	McDonald/Seattle criteria or Jones/Baltimore criteria	+	+	+	+	−	+
Thornley et al [40]	≥4 y	NR	+	−	+	+	+	−

HVOD indicates hepatic veno-occlusive disease; VOD, veno-occlusive disease; TRM, transplant-related mortality; OS, overall survival; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; NR, not reported; + yes; −, no.

*McDonald criteria: <30 days after HSCT, jaundice, hepatomegaly and right upper quadrant pain, ascites, and/or weight gain. Jones criteria: <21 days after HSCT, bilirubin >2 mg/dL, and 2 of the following: tender hepatomegaly, ascites, or weight gain >5% from baseline. Modified Seattle criteria: <20 days after HSCT, occurrence of 2 of the following events: bilirubin >2 mg/dL, hepatomegaly, or right upper quadrant pain of liver origin, unexplained weight gain (>2% of baseline body weight) because of fluid accumulation.

tween individuals. In consequence, many transplantation centers have adopted the use of intravenous busulfan and closer monitoring of serum levels in an effort to reduce HVOD and other transplant-related problems [43-46]. Further, cyclophosphamide is associated with HVOD and it has been suggested that monitoring and subsequent dosing of cyclophosphamide and its metabolites in context of cyclophosphamide/total body irradiation regimens may be beneficial [47]. The studies identified by our review only included patients undergoing myeloablative allogeneic HSCT. However, reduced intensity preparative regimens are increasingly used in allogeneic HSCT. The risk of HVOD in this setting may be similarly reduced [48].

There are other limitations in this review worth recognition. Although our review incorporated data that were available from published reports regarding our primary outcome, the investigators were not contacted to obtain unreported data on secondary outcomes. In addition, we acknowledge that other prophylactic agents have been used in the prevention of HVOD. However, studies combining other agents with UA were captured by, as evidenced by the inclusion of the trial by Park et al. Interestingly, a retrospective cohort study from the European Group for

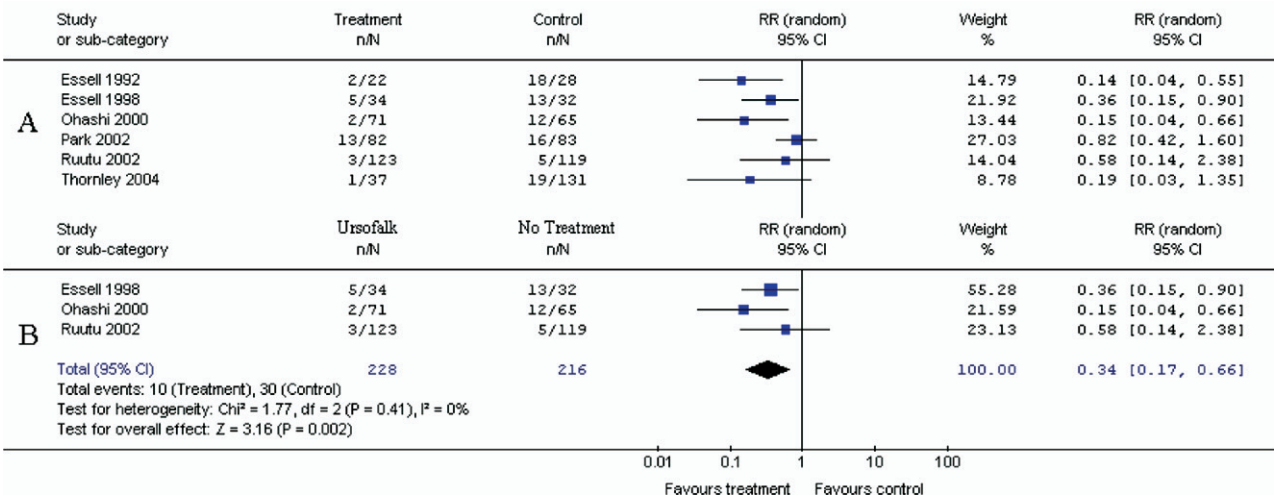

Figure 2. Forest plots of (A) hepatic veno-occlusive disease (primary outcome) in all studies and (B) pooled estimate of hepatic veno-occlusive disease from randomized trials. CI indicates confidence interval; RR, relative risk.

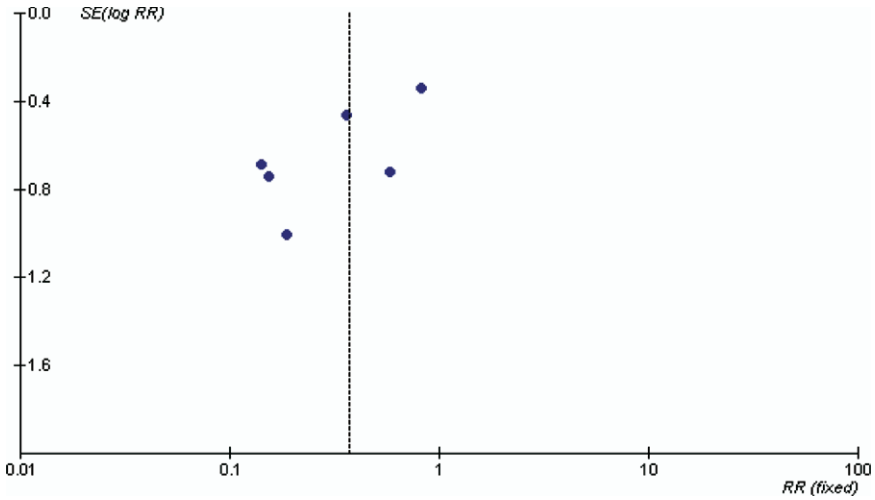

Figure 3. Funnel plot to assess publication bias using hepatic veno-occlusive disease as an outcome.

Blood and Marrow Transplantation [2] and a recent systematic review of prophylactic heparin in patients undergoing allogeneic HSCT did not demonstrate a benefit in terms of HVOD (pooled RR, 0.90; 95% CI, 0.62-1.29) [13]. Further, the potential for increased risk of bleeding in these high-risk patients remains a concern with agents that influence the coagulation system.

There has been much excitement around the use of defibrotide, a novel agent that has shown promise in the management of HVOD. Although its exact mechanism of action is unknown, its clinical effect may be

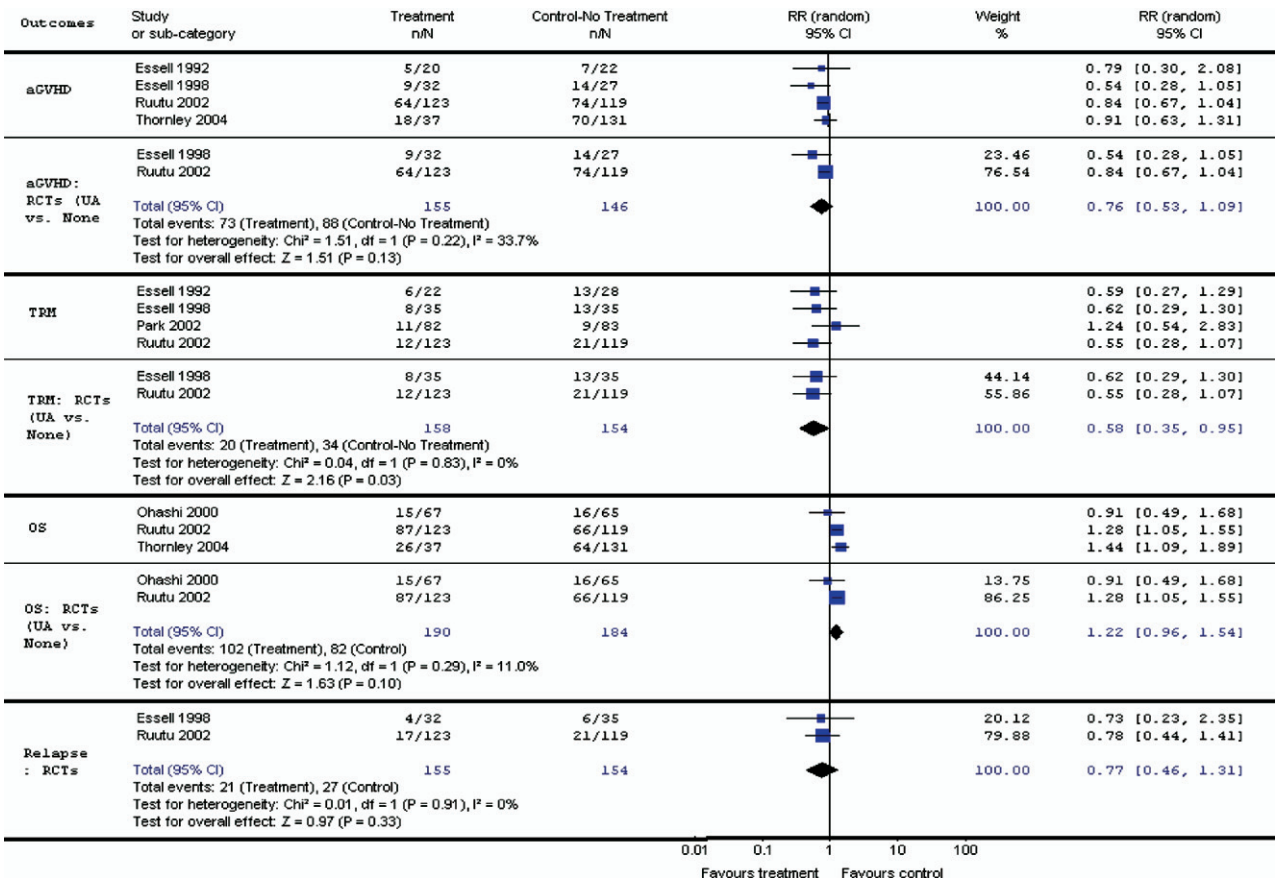

Figure 4. Forest plots of secondary outcomes. aGVHD indicates acute graft-versus-host disease; CI, confidence interval; OS, overall survival; RCT, randomized controlled trial; RR, relative risk; TRM, transplant-related mortality; UA, ursodeoxycholic acid.

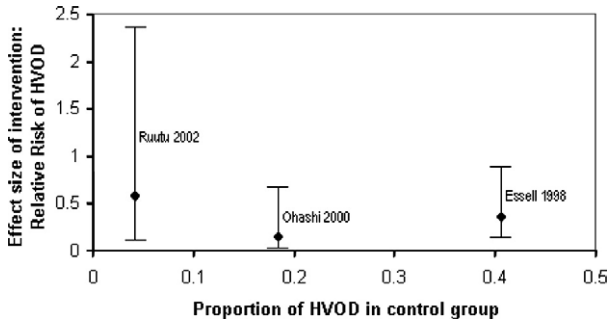

Figure 5. Point estimate of relative risk of hepatic veno-occlusive disease (HVOD) and 95% confidence interval in the 3 randomized trials comparing ursodeoxycholic acid with no treatment as compared with the proportion of HVOD in the control population.

mediated by altering the hemostatic balance at the endothelial level by causing endothelial release of tissue plasminogen activator [49], upregulation of the release of nitric oxide, prostaglandins I_2 and E_2 [50], thrombomodulin [51], decreased release of plasminogen activator inhibitor [52], stimulation of adenosine receptor [53], decreased thrombin generation, and decreased tissue factor activity and endothelin activity [54,55]. There have been numerous encouraging reports on its beneficial effects alone [56-62] or in combination with other agents [61,63-65] in the therapy of established HVOD. These studies were reviewed in a recent publication [55]. In contrast, the prophylactic use of defibrotide is less well studied, with no published randomized trials supporting its use. The largest published prophylactic trial was a single-institution study that compared 52 consecutive patients undergoing HSCT for hematologic malignancies with 52 historical controls [66]. All patients received heparin prophylaxis, with the experimental arm also receiving defibrotide. The investigators were able to demonstrate that the combined treatment of defibrotide and heparin reduced maximum bilirubin levels, the proportion of patients with HVOD, improved event-free survival, and trend toward improved 100-day mortality. We are aware of only 1 ongoing randomized trial that was conducted in the pediatric population to address defibrotide prophylaxis for HVOD (ClinicalTrials.gov Identifier: NCT00272948).

In summary, the favorable tolerance and ease of administering UA appear to be coupled with reductions in HVOD and TRM, as suggested in this systematic review. We suggest that UA should be considered as effective pharmacologic prevention of HVOD in adult patients undergoing allogeneic HSCT.

ACKNOWLEDGMENTS

J. Tay is a University of Ottawa Centre for Transfusion Research Fellow supported by the Canadian Blood Services. A. Tinmouth is supported by a Canadian Blood Services/Canadian Institute for Health Research New Investigator Research Award. D. Fergusson is supported by a Canadian Institute for Health Research New Investigator Research Award.

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